Linking Bistable Dynamics to Metabolic P Systems

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Summary. Bistability, or more generally multistability, is an important recurring theme in biological systems. In particular, the discovery of bistability in signal pathways of genetic networks, prompts strong interest in understanding both the design and function of these networks. Therefore, modelling these systems is crucial to understand their behaviors, and also to analyze and identify characteristics that would otherwise be difficult to realize. Although different classes of models have been used to study bistable dynamics, there is a lag in the development of models for bistable systems starting from experimental data. This is due to the lack of detailed knowledge of biochemical reactions and kinetic rates.
In this work, we propose a procedure to develop, starting from observed dynamics, Metabolic P models for multistable processes. As a case study, a mathematical model of the Schlögel's dynamics, which represents an example of a chemical reaction system that exhibits bistability, is inferred starting from observed stochastic bistable dynamics. Since, recent experiments indicate that noise plays an important role in the switching of bistable systems, the success of this work suggests that this approach is a very promising one for studying dynamics and role of noise in biological systems, such as, for example, genetic regulatory networks.

1 Introduction

Bistability is an important recurring theme in cell signaling and has been studied extensively through experiments, theoretical analysis, and numerical simulations [8, 10, 3, 22]. A bistable system has two distinct steady states and any initial state will eventually bring the system into one of them. Bistability is a key to understand basic cellular phenomena, such as decision-making processes in cell cycle progression, cell differentiation and apoptosis [2]. It is also involved in the loss of cellular homeostasis associated with early events in cancer onset [12] and

in prior diseases [11]. In [23], different bistable phenomena in bacteria and the importance of bistability for the origin of new species are studied.

Recently, interest grew in the investigation of the bistable dynamics regulations through differential and stochastic modelling [8, 10]. Usually, differential and stochastic models are developed based on detailed knowledge of biochemical reactions, molecule amounts and kinetic. Kinetic rates are estimated by using the mass action law, while stochastic parameters are derived from these rates.

However, there are several limitations for a reliable application of these classes of models. First, the determination of kinetic and stochastic constants depends on the chemo-physical details of the reactions, and moreover, even if carefully established in rigorous experimental settings, they may be completely different when many reactions are put together in real complex systems. Second, data availability and regulatory information usually can not provide a comprehensive picture of biological regulations. Lastly, in the processes with only a few molecules, classic mass action kinetics are no longer valid for describing the reaction dynamics. For these reasons, the modelling of observed dynamics is not a trivial work and in some cases it still remains an open problem.

Recognizing the importance of bistability in biochemical systems, some techniques to obtain mathematical models of bistable (multistable) systems starting from observed dynamics or experimental data are needed.

In this work, we propose a procedure, rooted in Metabolic P Systems [17, 15], shortly MP Systems, to infer models of an observed, also stochastic, bistable (multistable) dynamics.

As a case study, a mathematical model of the Schlögel's reaction [21], which represents an example of chemical reaction system that exhibits bistability, is inferred starting from observed stochastic dynamics. Since recent experiments indicate that noise and stochasticity play important roles in the switching of bistable systems, this work suggests that this approach is very promising for studying the dynamics and role of noise in biological systems, like, for example, genetic regulatory networks.

2 Metabolic P Systems and Log-Gain theory: a brief introduction

MP systems have been introduced as mono-membrane multiset rewriting grammars, whose rules are regulated by specific functions [15]. The aim is to control the matter transformation in a reactor by means of rules whose fluxes dynamically depend on the state of the system. This strategy of rules application is different to that of P Systems [20] and it has been successfully applied to several biological processes [1, 18, 19].

Specifically, an MP system is completely specified (the reader can find the formal definition in [17]) by: *i)* n substances and their initial values, *ii)* m reactions,

with[3] $m > n$, *iii)* m corresponding flux regulation functions, *iv)* k parameters[4], and their initial values, which are arguments, beside substances, of flux regulation functions, and *v)* k parameter evolution functions.

A *state* q is an $\mathbb{R}^{n+k}$ vector, reporting the current amounts of substances and parameters, while each rule r_j (with $j = 1, \ldots, m$) having some of the n substances as substrates and some as products, is associated with a couple of vectors $(r_j^-, r_j^+) \in \mathbb{N}^n \times \mathbb{N}^n$(one of which possibly null), reporting the substance quantities respectively occurring in the premise and in the consequence of r_j.

As an example, we can consider a system $\mathcal{M}$ with three substances $\{a, b, c\}$, two parameters $\{v, w\}$ which values evolve, for $t \in \mathbb{N}$, according with their own function $f_v(t)$ and $f_w(t)$, respectively, and four reactions:

$$\begin{aligned} r_1 &: ab \rightarrow aa \\ r_2 &: bcc \rightarrow a \\ r_3 &: ac \rightarrow \lambda \\ r_4 &: abc \rightarrow bb. \end{aligned} \tag{1}$$

The reactions (1) correspond to the following vectors, respectively :

$$\begin{aligned} &(r_1^-, r_1^+) = ((1,1,0),(2,0,0)),\ (r_2^-, r_2^+) = ((0,1,2),(1,0,0)), \\ &(r_3^-, r_3^+) = ((1,0,1),(0,0,0)),\ (r_4^-, r_4^+) = ((1,1,1),(0,2,0)). \end{aligned}$$

Four flux regulation functions, one for each rule, are defined from $\mathbb{R}^5$ to $\mathbb{R}$, and they produce at each step *fluxes* u_1, u_2, u_3, u_4, associated with the corresponding reaction.

We call *stoichiometric matrix*, the $(n \times m)$-dimensional matrix $\mathbb{A}$ formed by the vectors $r_i^+ - r_i^-$, for every rule r_i, disposed according to a prefixed order. For example, in the system above, we have

$$\mathbb{A} = \begin{pmatrix} 1 & 1 & -1 & -1 \\ -1 & -1 & 0 & 1 \\ 0 & -2 & -1 & -1 \end{pmatrix}. \tag{2}$$

The stoichiometric matrix is assumed to have maximal rank. Should we have one row linearly dependent on the others, we could delete it (together with the corresponding substance in the system, as studying its dynamics would not add any useful information on the system), and analyse only the remaining substances (we newly say n) and the corresponding $n \times m$ stoichiometric matrix which now has full rank.

[3] We assume $m > n$, as it realistically happens in biochemical systems. A few examples are given by the following protein-protein interaction networks: yeast has 8868 known interactions among 3280 proteins [9], Drosophila has 4780 known interactions among 4679 proteins, and C. elegans has 5534 known interactions among 3024 proteins [7].

[4] Parameters are internal or external controlling variables which somehow affect the system's functioning.

Let $U[t] = (u_r[t] \mid r \in R)$ be, for $t = 0, 1, \ldots$, the (m)-dimensional column vector of fluxes and $X[t]$ be the (n)-dimensional column vector of substances. Then, the dynamics of an MP system, given by both the evolution of parameters, according to their laws, and by the evolution of the substances, are computed by the *Equational Metabolic Algorithm*[15, 14], which is the following recurrent n-equations system:

$$X[t+1] = \mathbb{A} \times U[t] + X[t] \tag{3}$$

where $\times$ denotes the ordinary matrix product and t the discrete instant of time.

This way to observe the evolution rules of a system reproducing a biological reaction has been proposed in [1] and constitutes a new perspective. In fact, by using MP systems, one assumes an a priori choice of the time interval τ, between consecutive evolution steps, that depends on the macroscopic level at which considering the dynamics of the system. Then, the flux values, depending on the state of the system, are computed according to the chosen observation granularity.

Therefore, the approach of modelling by MP systems considers the rules as macroscopic matter transformation reactions rather than microscopic molecular interactions. Then, the search of fluxes is aimed at designing a model of the observed macroscopic reality with respect to the abstract transformations one has assumed, and it is different from the rate estimation typically studied in systems biology.

This inverse dynamical problem is the starting point of the Log-Gain theory [16]. The goal of this theory is to deduce the time-series of fluxes, reproducing an observed dynamics and biologically meaningful, starting from some consecutive (at a time interval τ) time-series of the state of a system. When such time-series are known, the discovery of flux regulation functions is a problem of approximation which can be solved with mathematical regression techniques.

According to the simplest formulation of this theory, given a number of observations of the system's states, for which the stoichiometry is known, the relative variations of any reaction flux of the rule $r_j : \alpha_j \rightarrow \beta_j$ is the sum of the relative variations of its reactants, plus some error p_j, called *reaction offset*, which is introduced as a variable of the system:

$$(u_j[t+1] - u_j[t])/(u_j[t]) = \sum_{x \in \alpha_j} ((x[t+1] - x[t])/x[t]) + p_j.$$

We denote with $P[t]$ the m-dimensional vector of p_j variables, $j = 1, \ldots, m$, that is, of the errors introduced with the log-gain approximations of fluxes at step t. Furthermore, we denote with $Lg(U[t])$ the m-dimensional vector of relative fluctuations, that is $((u_j[t+1] - u_j[t])/u_j[t] \mid j = 1, \ldots, m)$, for any $t \in \mathbb{N}$. Analogously, $Lg(X[t])$ is the vector of relative variations of substances. Therefore, in formal terms, the $m+n$ equations system we want to solve (in order to find the vector U[t+1]) is

$$\begin{cases} Lg(U[t]) = \mathbb{B} \times Lg(X[t]) + C \cdot P[t+1] \\ \mathbb{A} \times U[t+1] = X[t+2] - X[t+1] \end{cases} \tag{4}$$

where $\mathbb{B}$ is a $(m \times n)$-dimensional boolean matrix selecting, by matrix product, the reactants for each reaction, and C is an m-dimensional boolean vector selecting, by Schur product, only n of the m reaction offsets (hence that are n other unknowns in the system, besides the m fluxes). As proposed in [4], vector C selects a set of n linear independent reactions, called *covering set*, in order to infer the flux time-series. However, a way to choose the best covering set among the linearly independent ones still remains to be found.

3 A flowchart to infer bistable MP systems

In order to model bistable (stochastic) phenomena starting from experimental data, we propose the flowchart represented in Figure 1. In our method, first a set of intermediate MP systems having dynamics in accordance with several observed dynamics is created, by using Log-Gain theory, least-square theory and correlation analysis. In the case of stochastic phenomena, this phase in particularly important because it allows us to obtain dynamics having behaviours, in particular those related to the reaction fluxes, not affected by observed noise. Namely, first *i)* we apply the Log-Gain theory to infer the numeric values of the reaction fluxes, then *ii)* a correlation analysis is used to suggest relationships between flux and substance/parameter time-series, and finally *iii)* least-squares theory is used to approximate the flux regulation functions.

Once we obtained good approximations of the different observed dynamics, we apply again the least-squares theory to infer an unique MP system modelling the bistability of the input phenomenon.

This last phase represents the major challenge because it needs a mathematical analysis to identify the appropriate forms of the final flux regulation functions. As result of this flowchart, we will obtain an MP system $\mathcal{M}$ modelling the bistability of the studied phenomenon.

In the following section we will apply this flowchart to a chemical reaction system which exhibits a stochastic bistable dynamics.

4 A case study: the stochastic Schlögel's reaction

An interesting example of bistable process is provided by the Schlögel's model [21], which is an autocatalytic, trimolecular reaction schema composed of the set of coupled chemical reactions reported in Table 1.

What makes the Schlögel's reaction especially interesting is that, despite its simplicity (it is composed of four reactions involving three species, two of which are buffered) it provides a very rich dynamics. If we fix the stochastic parameters (and hence the reaction rates which can be computed from them), according to certain ranges of values, as well as the initial amounts of the two buffered species a and b, depending on the initial amount of x, the stochastic simulation of the system provides a bistable behaviour.

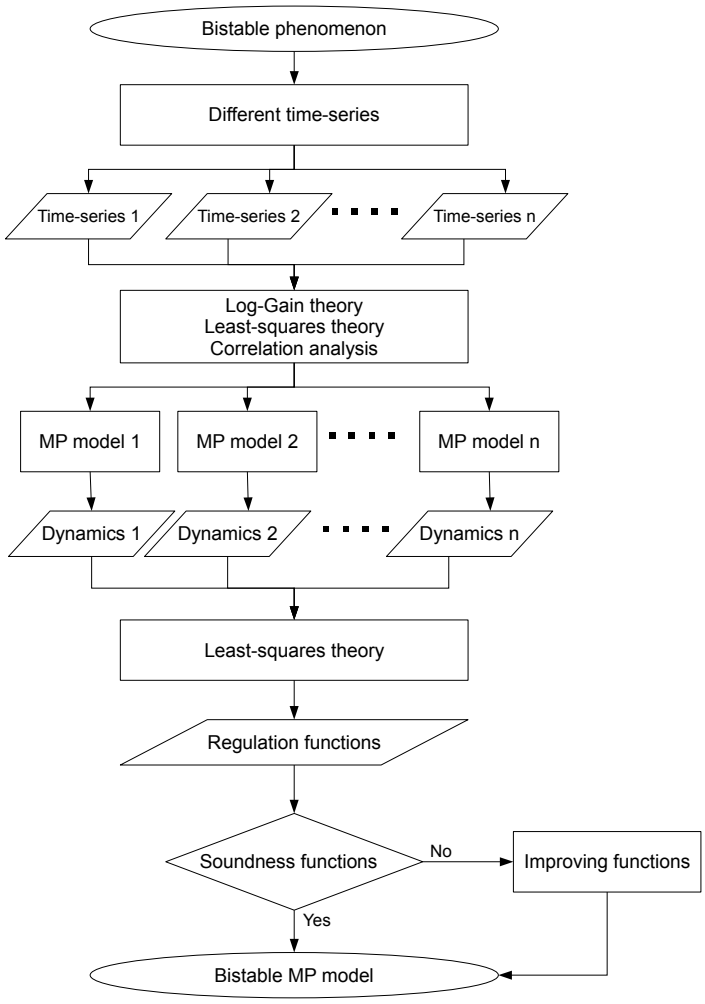

Fig. 1. Flowchart for the estimation of an MP system describing the dynamics of a bistable (stochastic) phenomenon. Experimental data are analysed and used to infer intermediated MP models which characterize the different observed dynamics. Then, these models are used to generate reaction flux and substance dynamics in accordance with the observed ones. Finally, these dynamics represent the input of a least-squares analysis, where, by using also some hypothesis about the logic governing the studied phenomenon, the final MP system is inferred.

Let $\#X[t] = (\#x_1[t], \#x_2[t], \ldots, \#x_n[t])$ be the vector representing the state of the system (i.e. the number of molecules of every species x_i in the system

Reactions	Stochastic parameters
$r_1 : a + 2x \to 3x + a$	$c_1 = 3 \cdot 10^{-7}$
$r_2 : 3x \to 2x$	$c_2 = 1 \cdot 10^{-4}$
$r_3 : b \to x + b$	$c_3 = 1 \cdot 10^{-3}$
$r_4 : x \to \lambda$	$c_4 = 3.5$

Table 1. Schlögel's reactions and a set of stochastic parameters [13].

evaluated at time t, for $i = 1, ..., n$). In our simulations, we used the set of stochastic parameters given in Table 1 and we performed, by using the *Stochastic Simulation Algorithm* [5, 6], shortly *SSA*, up to 40 independent simulations from $t = 0$ starting from the following initial configurations:

$$\begin{aligned} \#X[0] &= (\#a[0], \#b[0], \#x[0]) = (1 \cdot 10^5, 2 \cdot 10^5, 0) \\ \#X[0] &= (\#a[0], \#b[0], \#x[0]) = (1 \cdot 10^5, 2 \cdot 10^5, 238) \\ \#X[0] &= (\#a[0], \#b[0], \#x[0]) = (1 \cdot 10^5, 2 \cdot 10^5, 800). \end{aligned} \tag{5}$$

The average behaviours (i.e. simulations were sampled with constant rate and an average concentration of species x over the up to 40 different stochastic simulations starting from the same initial state was computed) of the species x, according to different initial states, are reported in Figures 2 and 3. The left-hand part of Figure 2 shows that if we simulate the Schlögel's model starting from the initial state $(1 \cdot 10^5, 2 \cdot 10^5, 0)$ then the number of molecules of species x goes up until it reaches a stable 'on' state. Alike, the right-hand part of the same Figure shows that if we simulate it starting from the initial state $(1 \cdot 10^5, 2 \cdot 10^5, 800)$ then the number of molecules of species x decreases and stabilizes at stable 'off' state. Moreover, if we start the simulations from the initial state $(1 \cdot 10^5, 2 \cdot 10^5, 238)$, the number of molecules of x randomly stabilizes at one of the two possible distinct stable states. These behaviours are depicted in Figure 3.

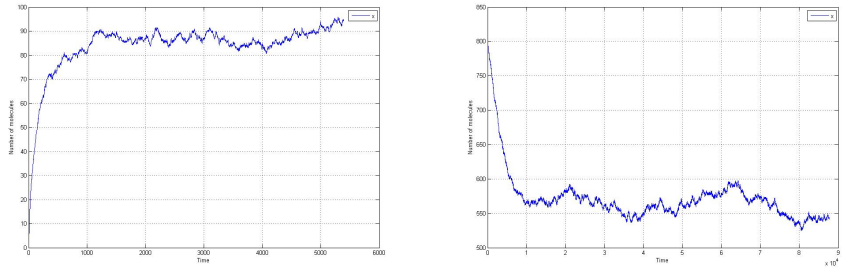

Fig. 2. Average time-evolution of species x in the Schlögel model obtained by using the SSA and considering the initial states $(1 \cdot 10^5, 2 \cdot 10^5, 0)$ (leftmost image) and $(1 \cdot 10^5, 2 \cdot 10^5, 800)$ (rightmost image).

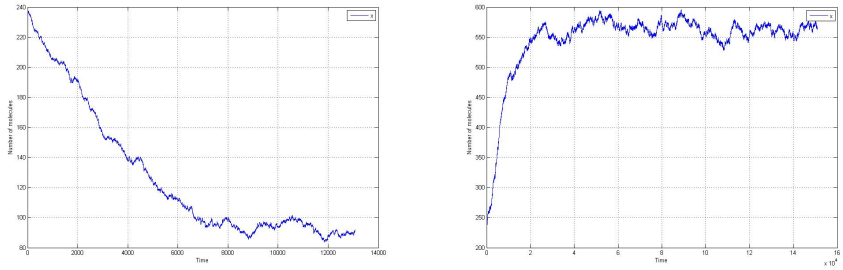

Fig. 3. Average time-evolution of species x in the Schlögel by using the SSA with initial state $(1 \cdot 10^5, 2 \cdot 10^5, 238)$. The two different behaviours are the result of the bimodal probability distribution of the set of reactions.

4.1 Results of the flowchart

In this subsection we will see the result obtained by applying our method to infer an MP system modelling the stochastic bistability of the Schlögel model.

Obtaining data.

The Schlögel's reaction has been simulated by considering the three different initial states (5) to generate the time series of species x. Then, we clustered the data of the different behaviours in four sets and we calculated the average number of molecules during all the steps of the time evolution. In particular, these were sampled at regular time intervals to mimic experimental measurements.

Inferring intermediate MP models.

First, we computed reaction fluxes by applying the Log-Gain theory with different plausible covering sets [4], concluding that r_3 has a constant flux. This result is in accordance with the nature of this reaction, which has a buffered reactant. After that, considering the four behaviours, we applied the least-squares theory to infer four sets of flux regulation functions, that is, to obtain four MP grammars. In particular, according to a correlation analysis, and given that a and b are buffered species, we assumed that each functions $\varphi_j(q)$, $j = 1, 2, \ldots, 4$, can be seen as:

$$\varphi_j(q) = \begin{cases} \alpha_j + \beta_j x & \text{if } j = 1, 2, 4 \\ \alpha_j & \text{if } j = 3. \end{cases} \tag{6}$$

In this way, we obtained four MP systems, reported in Tables 2, 3, 4 and 5, which characterize the different behaviours showed in Figures 2 and 3.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = 3.4710 \cdot 10^{-3} + 4.1533 \cdot 10^{-1}x$
$r_2 : 3x \to 2x$	$\varphi_2 = 4.7307 \cdot 10^{-1} + 4.0487 \cdot 10^{-1}x$
$r_3 : b \to x + b$	$\varphi_3 = 0.87437$
$r_4 : x \to \lambda$	$\varphi_4 = 1.2542 \cdot 10^{-4} + 1.5008 \cdot 10^{-2}x$

Table 2. Flux regulation functions approximating the behaviour of Schlögel's reaction computing by the SSA, starting from the initial state $\#X[0] = (1 \cdot 10^5, 2 \cdot 10^5, 0)$, that is, the behaviour of the species x showed in the left part of Figure 2.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = -2.1926 \cdot 10^{-13} + 2.5331 \cdot 10^{-4}x$
$r_2 : 3x \to 2x$	$\varphi_2 = 7.1050 \cdot 10^{-1} - 2.9884 \cdot 10^{-4}x$
$r_3 : b \to x + b$	$\varphi_3 = 0.87437$
$r_4 : x \to \lambda$	$\varphi_4 = 2.5415 \cdot 10^{-13} + 8.4015 \cdot 10^{-4}x$

Table 3. Flux regulation functions approximating the behaviour of Schlögel's reaction computing by the SSA, considering the initial state $\#X[0] = (1 \cdot 10^5, 2 \cdot 10^5, 800)$, that is, the behaviour of the species x showed in the right part of Figure 2.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = -1.2646 \cdot 10^{-15} + 8.5151 \cdot 10^{-4}x$
$r_2 : 3x \to 2x$	$\varphi_2 = 8.5511 \cdot 10^{-1} - 1.7333 \cdot 10^{-3}x$
$r_3 : b \to x + b$	$\varphi_3 = 0.87437$
$r_4 : x \to \lambda$	$\varphi_4 = 5.7823 \cdot 10^{-15} + 2.8242 \cdot 10^{-3}x$

Table 4. Flux regulation functions approximating the behaviour of Schlögel's reaction dynamics depicted in the left part of Figure 3.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = -1.6164 \cdot 10^{-13} + 1.7453 \cdot 10^{-3}x$
$r_2 : 3x \to 2x$	$\varphi_2 = 8.1220 \cdot 10^{-1} + 1.7921 \cdot 10^{-3}x$
$r_3 : b \to x + b$	$\varphi_3 = 0.87437$
$r_4 : x \to \lambda$	$\varphi_4 = -7.8644 \cdot 10^{-16} + 6.3066 \cdot 10^{-5}x$

Table 5. Flux regulations functions approximating the behaviour of Schlögel's reaction dynamics depicted in the right part of Figure 3.

Inferring a bistable MP system.

In this phase we used the four intermediate MP models as starting points to obtain an MP system $\mathcal{M}$ describing the bistable behaviours of the Schlögel's model. In particular, we followed these steps: *i)* we computed the dynamics of the four MP systems to obtain four time-series of x and u_1, u_2, u_3 and u_4, respectively, *ii)* we approximated the flux regulation functions, starting from the time-series obtained in the previous step, by using the least square theory, *iii)* we analyzed the inferred functions, and *iii)* finally we obtained the final MP grammar of $\mathcal{M}$.

The Schlögel's model has four reactions, each of which is equipped with a function describing how that reaction contributes to the change of the number of molecules of x: $\varphi_1(q)$, $\varphi_2(q)$, $\varphi_3(q)$, and $\varphi_4(q)$, respectively.

Since the Schlögel's model is a one-variable system, an MP system modelling it can be expressed, considering the stoichiometry of each reaction, as the sum of the four fluxes:

$$x[i+1] - x[i] = \sum_{i=1}^{4} (r_i^+ - r_i^-)\varphi_i(q) = f(q). \tag{7}$$

To describe a bistable behaviour, equation (7) needs an unstable steady state to separate the attractor regions of two stable steady states [24], so we need a function $f(q)$, called the *global flux function* of x, having at least three steady states to realize an MP system describing the bistability of the studied process.

The simplest function $f(q)$ with three zeros is the cubic polynomial. Therefore, since the fluxes of reaction r_3 are constant, we assumed the following forms for the flux regulation functions of $\mathcal{M}$:

$$\varphi_j(q) = \begin{cases} \alpha_j + \beta_j x + \gamma_j x^2 + \eta_j x^3 & \text{if } j = 1, 2, 4 \\ \alpha_j & \text{if } j = 3 \end{cases} \tag{8}$$

and we applied the least square theory to learn the coefficients of each function, obtaining the MP grammar reported in Table 6, which models the bistable behaviour of the Schlögel's model. To prove this, if we consider such flux regulation functions, $f(q)$ can be reduced as follow:

$$f(q) = c_1 x^2 + c_2 x^3 + c_3 + c_4 x \tag{9}$$

where:

$$\begin{aligned} c_1 &= \sum_{j=1}^{4} \gamma_j = 1.0480 \cdot 10^{-6} & c_2 &= \sum_{j=1}^{4} \eta_j = -1.1130 \cdot 10^{-9} \\ c_3 &= \sum_{j=1}^{4} \alpha_j = 1.9370 \cdot 10^{-2} & c_4 &= \sum_{j=1}^{4} \beta_j = -2.6800 \cdot 10^{-4}. \end{aligned} \tag{10}$$

The set of parameters $\{c_j \mid j = 1, 2, \ldots, 4\}$ is associated with a bistable dynamics, that is, two stable steady states separated by an unstable state. By using the discriminant analysis, we can analyze the nature of the roots of a polynomial. The discriminant of (9) is given by:

$$\Delta = c_1^2 c_4^2 - 4c_2 c_4^3 - 4c_1^3 c_3 - 27c_2^2 c_3^2 + 18 \prod_{j=1}^{4} c_j. \tag{11}$$

For a cubic polynomial we have the following cases: *i)* if $\Delta > 0$ then the polynomial has 3 distinct real roots, *ii)* if $\Delta < 0$ then the polynomial has 1 real root

and 2 complex conjugate roots, and *iii)* if $\Delta = 0$ then at least 2 polynomial's roots coincide, and they are all real. The cubic polynomial in (9) has $\Delta = 4.5012 \cdot 10^{-22}$, so such function has three different roots. Moreover, to realize a stable 'on' state the sign of the cubic term needs to be a minus. For three different non-negative steady states a positive quadratic and a negative linear term are needed. In addition if a positive constant is adjoint, then the one-variable system:

$$x[i+1] - x[i] = -k_1 x^3 + k_2 x^2 - k_3 x + k_4, \quad k_i > 0, \quad i = 1, 2, 3, 4. \tag{12}$$

has two positive stable steady states [25].

It is simple to see that equation (9), considering the constants (10), is in accordance with (12). Then the MP grammar of Table 6 models the bistable dynamics of the Schlögel's reaction, which has two positive stable steady states.

However, we saw that, starting from some initial states, we obtained negative fluxes. Therefore, we applied the last phase of our flowchart to obtain a final "good" set of functions.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = 47.133 - 3.5489 \cdot 10^{-1} x + 7.8941 \cdot 10^{-4} x^2 - 5.4356 \cdot 10^{-7} x^3$
$r_2 : 3x \to 2x$	$\varphi_2 = 46.103 - 3.4186 \cdot 10^{-1} x + 7.6346 \cdot 10^{-4} x^2 - 5.2949 \cdot 10^{-7} x^3$
$r_3 : b \to x + b$	$\varphi_3 = 0.87437$
$r_4 : x \to \lambda$	$\varphi_4 = 1.885 - 1.2762 \cdot 10^{-2} x + 2.4902 \cdot 10^{-5} x^2 - 1.2957 \cdot 10^{-8} x^3$

Table 6. Bistable MP grammar modelling the Schlögel's reaction.

Improving flux regulation functions

First, by considering equation (12), we assumed that, since $c_i > 0, i = 1, 3$ then the monomials $c_1 x^2$ and the constant c_3, are associated with reactions producing x. Since r_3 has b as reactant, which is a buffered species, and $u_3[t]$ is constant for $t = 0, 1, \ldots$, then $\varphi_3(q) = c_3$. This implies that $\varphi_1(q) = c_1 x^2$, which is in accordance to the fact that r_1 is a double-molecular reaction. Similarly, $c_i < 0, i = 2, 4$, therefore $c_2 x^3$ and $c_4 x$ can be seen as functions regulating the fluxes of reactions consuming x. Since, r_2 and r_4 are tri-molecular and an one-molecular reaction respectively, we assumed that $\varphi_2(q) = c_2 x^3$ and $\varphi_4(q) = c_4 x$. In this way, we obtained the MP grammar reported in Table 7, which computes the same dynamics of the grammar of Table 7, but having flux time-series positive for each initial states.

5 Conclusion and ongoing work

Schlögel's model is an example of chemical reaction system which exhibits bistability. Bistable behaviour can be found in many biological networks, including heart models, visual perception and gene networks.

Reaction	Maps
$r_1 : a + 2x \to 3x + a$	$\varphi_1 = 1.0480 \cdot 10^{-6} x^2$
$r_2 : 3x \to 2x$	$\varphi_2 = 1.1130 \cdot 10^{-9} x^3$
$r_3 : b \to x + b$	$\varphi_3 = 1.9370 \cdot 10^{-2}$
$r_4 : x \to \lambda$	$\varphi_4 = 2.6800 \cdot 10^{-4} x$

Table 7. Bistable MP grammar modelling the Schlögel's reaction.

Owing to the ubiquity and importance of switching behaviours, it is important to have comprehensive mathematical models of bistable chemical reaction systems. In particular, there is a lag in the development of models for bistable systems starting from experimental data. This is due to the lack of detailed knowledge of biochemical reactions and kinetic rates.

In this work, we used the Schlögel's model as an example to study the applicability of the MP Systems to infer mathematical models describing observed bistable (multistable) dynamics. The theoretical background of this approach comes from the Log-Gain theory for MP systems, which links observed time-series to the MP systems for simulating and analyzing dynamics of phenomena in living cells. Compared with approaches based on stochastic models and mass action law, our approach allows to obtain some insights into the logic governing a bistable phenomenon starting from observations of such a phenomenon.

Starting from stochastic dynamics of the Schlögel's model, we saw the possibility to obtain an MP system describing the bistability of such dynamics. Since, different studies indicates that noise plays an important roles in the switching of bistable systems, the results of this work suggests that the proposed approach is a very promising one for inferring and studying bistable and multistable dynamics of biological systems, also when kinds of noise are present. Moreover, this approach could be very useful in the cases of complex reaction networks, for which data availability and regulatory information can not provide a comprehensive picture of the role of the diverse reactions in the toggle switch transition.

Ongoing research is focused on the application of the proposed approach to infer bistable systems inspired from biology and chemistry and analyze the logic governing these systems. In particular, since bistable switches are common motifs in genetic regulatory networks, we have a mind to apply our procedure for modelling a naturally occurring switch from relatively few experimental data points, yielding a model suited: *i)* to dynamical simulation, *ii)* to give predictions of unmeasured proteins and genes of the analyzed network, *iii)* to analyze the effects of noise and perturbations which can afflict the network, *iv)* and to develop robust mathematical models which could represent prototypes of synthetic biological systems.

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